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Nanoneuromedicine for management of neurodegenerative disorder

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ABSTRACT

Conventional drug delivery systems are inadequate in providing essential cyto-architecture restoration and connection patterns because of restrictions posed by the restrictive blood-brain barrier. Nanotechnological approaches involve various nano-sized carrier systems and other devices, which stimulate the action of therapeutic agents on molecular level and revolutionized the treatment and diagnosis of neurodegenerative disorders with minimal side effects. Over the conventional approaches, nanotechnological approaches have various promising strategies to cross blood brain barrier and increase the bioavailability of therapeutics in brain. This review article emphasizes the current and future utility of nano drug delivery systems for the treatment of various neurodegenerative disorders.

1. Introduction

Neurodegenerative disorders (NDs) inscribe the progressive damage of neurons, usually concerned with death of neuronal cells. Various types of NDs like Alzheimer's (AD), Parkinson's (PD), Prion (PrD) disease and Amyotrophic Lateral Sclerosis (ALS) are associated with the neuronal damage in the different areas of brain and spinal cord. At present the available diagnosis and treatment strategies for NDs are inadequate to inhibit the progression of the brain injury or degeneration. The blood-brain barrier (BBB) appeared as one of the most arduous hurdles for the transport of therapeutic or imaging contrast agent into the nervous system [1–4]. While the available potentials for imaging and therapy of brain disorders mostly depend on the vascular and penetration ability across the BBB [5–7], for the rectification of these problems, a novel, safe and more sensitive imaging modality with improved therapeutic potential is immediately required. The nanoneuromedicine offer innovative and promising approaches to address the NDs as well as other nervous system diseases for which limited options are available [8].

Theranostics, the nanotechnology-based devices, have ability to deliver therapeutic, imaging and diagnostic agents at a time [9]. However current practices of nanotechnology in pharmaceutical field have been represented in Fig. 1Aand B. Nanomedicine and other related technologies improve transportation of biological active/imaging/contrast agents from the BBB; increase the drug-carrier bond with clearance of pathogens from nervous system [10]. At present various types of nanomaterials are available with different physicochemical and therapeutic properties. The nanomedicines have tremendous positive features like greater chemical or biological substantiality, incorporating capability for hydrophilic as well as hydrophobic molecules, can be used in the treatment or diagnosis of various NDs (Table 1). In addition, the nanomedicines can administer from several routes like olfactory, oral and systemic etc. This review highlights variety of features of nano technological approaches involved in the treatment and prognosis of various NDs.

1.1. Latest developments in nanotechnology, nanomaterials and nanoarchitectonics

Recently, in the field of nanomedicine Li et al. developed layer-by-layer self-assembled stacked Testudo-like MoS2-NS superstructures carrying doxorubicin (Dox) and DNA oligonucleotides, which was considered as a base platform, achieving high efficacy and autonomous ATP responsive drug delivery [11,12].

Single walled carbon nanohorns (CNHs) are graphene-based tubules having 25 nm diameter and 4050 nm length. In medical field, their potential uses are in drug delivery, diagnosis, and clinical tests. Nakamura et al. developed micelles based drug delivery system by dispersing CNH in phospholipid poly(ethylene glycol) (PLPEG) and revealed the effect of PLPEG quantity on the cytotoxicity of PLPEG-CNH

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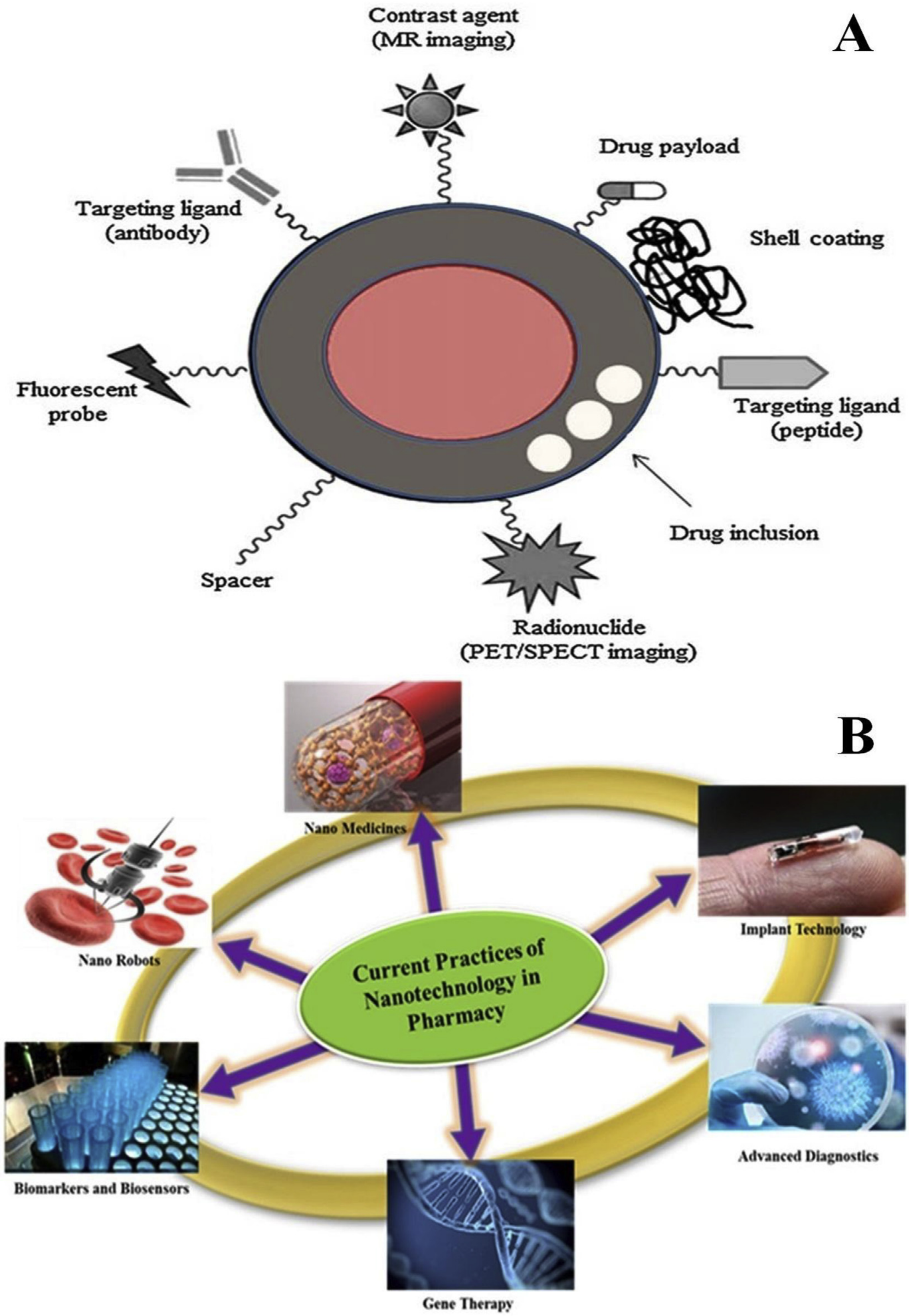

Fig. 1. (A) Graphical representation of theranostics system; (B) Current application of theranostics nanotechnology in pharmaceutical field.

in RAW264.7 mouse macrophages. The optimum PLPEG:CNH weight ratio was found to be 0.5:1 and 1:1. At the higher or lower ratios, the PLPEG-CNH toxicity and the macrophage uptake quantity increased and large agglomerates appeared [13].

Carbon nanotubes (CNTs), one of the emerging members of carbon family are potentially used in sensing, bone scaffolds, drug and gene delivery, composite materials, and water purification. The credit for successful applications of CNTs goes to desired conductivity, specificity, selectivity, high aspect ratio, high porosity and loading, ease in surface modification, and non-toxicity [14].

Radioisotopes are frequently used for various medical applications. Nowadays, a considerable quantity of ^{99m}Tc is generated in hospital using ^{99}Mo/^{99m}Tc generators. In this regard, Saptiama et al. prepared mesoporous alumina (MA) materials as potential adsorbents for molybdenum (Mo) using a soft-templated method. The change in calcination temperature from 600 to 900 °C improved the crystallinity but

Table 1
Overview of various neuro-therapies and interventions for CNS disorders.

Disorder	Type of Nanostructure	Therapeutic Agents	Mechanism of Action	Reference
Alzheimer's disease	Polymeric nanoparticles	Poly(alkyl cyanoacrylate) and poly(lactic acid) NPs	These engineered long-circulating NPs may have the ability to capture the toxic forms of the Aβ(1–42) peptide from the systemic circulation and potentially improve Alzheimer's disease condition through the proposed "sink effect".	[167]
	Poly(propylene imine) (PPI) glycodendrimers	Electroneutral maltose shell	Modify the total burden of β-amyloid	[168]
	Dendrimer	Lysine base	Protect cells against Aβ-induced cytotoxicity and K^+ channel modulation	[169]
	Chitosan nanoparticles	Tacrine	Release of drug from nanoparticles was diffusion-controlled	[170]
	Polymeric nanoparticle	Curcumin	Decreased levels of H_2O_2, increased glutathione (GSH) concentrations and create redox intracellular environment	[171]
	Nanoparticles	Curcumin	Curcumin nanoparticles increase neuronal differentiation by activating the Wnt/β-catenin pathway, involved in regulation of neurogenesis	[172]
Parkinson's disease	Lactoferrin (Lf) conjugated polyethylene glycol-polylactide-polyglycolide (PEG-PLGA) nanoparticle (Lf-NP)	Urocortin	Lf-NP effectively attenuated the striatum lesion	[118]
	Poly(ethylene glycol)–poly(lactic-co-glycolic acid) (PEG–PLGA) nanoparticles	Urocortin peptide (UCN)	OL modification increased the brain delivery of nanoparticles and enhanced the therapeutic effects of UCN-loaded nanoparticles on Parkinson's disease	[117]
	Poly-L-lysine (DGL) dendrigraft/NPs	Gene encoding human glial cell line-derived neurotrophic factor (*hGDNF*), DPA/*hGDNF*	Improved locomotor activity and apparent recovery of dopaminergic neurons	[173]
	Dendrimers	L-DOPA	DOPA dendrimers showed an increased aqueous solubility and enhanced photostability	[174]
	Dendrimers	Viologen-phosphorus	Viologen-phosphorus dendrimers inhibit ASN fibril formation	[121]
	PAMAM G4 dendrimer	PAMAM G4 dendrimer	Increase in tyrosine residue fluorescence, and inhibited fibrillation of ASN	[119]

decreased the surface area and the pore volume of the MA materials. These results can guide the design of effective Mo adsorbents based on mesoporous materials toward ^{99}Mo/^{99m}Tc generator preparation [15].

Nanoarchitectonics involves architecting of materials in the nanoscale. There are two types of bio-related nanoarchitectonics i.e. DNA nanoarchitectonics and cell macromolecular nanoarchitectonics. The former involves functionalization of single DNAs by chemical method to achieve stronger DNA binding, DNA aptamers and DNAzymes. Programmable assemblies of DNAs find their applications for selective labeling of biomaterials in cells and in animals, delivery of drugs to target sites and sensing in vivo. The later involves the construction of highly organized synthetic/natural macromolecular modified hybrid biointerfaces [16,17].

2. Nanotechnology across the BBB

The BBB is a physical and biological occlusion present in amid of central nervous system (CNS) and systemic blood circulation, protects brain from unwanted substances and other intruders [18]. The BBB contains endothelial cells, smooth muscle cells, pericytes, microglial cells and astrocytes with a tight junction amongst them and restrict the transcellular flux (Fig. 2A) [19–21]. Currently, nanotechnology appears as promising strategy in which the nanomaterials interact with BBB at molecular level and transport across the BBB through existing mechanisms (Fig. 2B) [20,22], without any intervention in the usual function of BBB and itself [23]. The nanomaterials have transcellular movement from blood to brain across the BBB with transcytosis movement involve receptor as well as adsorption mediated mechanism [24]. To achieve brain targeting across the BBB, the nanomaterials must have many competencies like minimum surface area, prolonged half-life in blood, nontoxic, biodegradable, biocompatibility, non-inflammatory and non-immunogenic with avoidance of reticulo-endothelial system (Table 2) [25–29]. The vital features of nanomaterials are depicted in Fig. 3.

2.1. Adsorptive-mediated transcytosis

Adsorptive-mediated transcytosis lead to electrostatic interaction of a ligand with the luminal surface charges of endothelial cells. The fabrication cell penetration peptides (e.g. TAT-derived peptides) and cationic proteins (e.g. albumin) on the surface of nanomaterials facilitate the passage across the BBB [24,30]. Thus, the addition of different domains like glycosylation [31], methylation [32] PEGylation [33–38], lipophilic domains [39,40], virus glycoprotein [41,42] or coating with polysorbates [24] on the surface of different types of nano devices lead to an enhanced penetration potential across the BBB. The diffusivity of nano devices across the BBB, several times depends on the material used in the coating, charge of the surface and the matrix of these particulate systems. An albumin coating, reduce the interaction between extracellular space proteins and decrease the size effect on the distribution of nanospheres [40,43]. Thus, these nanocarriers have greater optimization in convection enhanced delivery (CED) [42,44].

2.2. Receptor-mediated transcytosis

Receptor mediated transcytosis is more intensively explored physiological procedure. This involves the transportation of various nanomaterials across the BBB based on affinity towards the receptors of BBB cells. Receptor mediated transcytosis is achieved by addition of some specific proteins such as insulin [45], transferrin [46], apolipoprotein [47,48], macro-globins and other small peptides that are able to act as ligands for the receptors located on cells of BBB.

Certain monoclonal antibodies (mAbs) undergo receptor mediated transcytosis and are directed towards the receptors on BBB. Like the binding of OX26,8D3 & R17217 mAbs with transferrin, receptors recognize different epitopes and avert the competition with innate

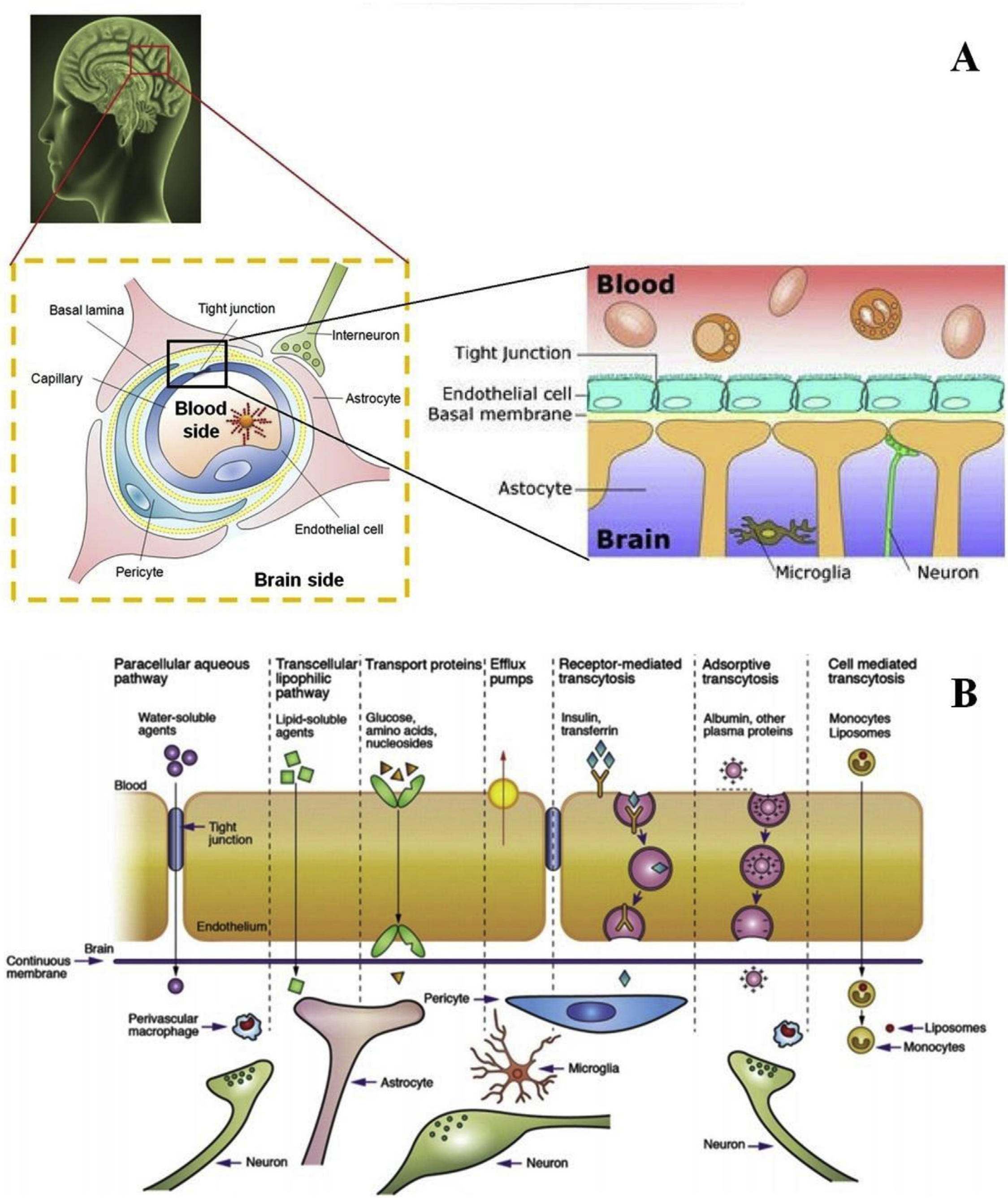

Fig. 2. (A) An insight of blood brain barrier (BBB); (B) Schematic representation of different transport pathways across the BBB [166].

transferrin in blood [49]. On the other hand, some mAbs involved in construction of brain targeted drug delivery devices are directed against insulin receptors [50].

3. Nanotechnology for AD

Literature suggests that AD affects more than 24 million people worldwide. Alzheimer's disease lead to onward loss or deterioration of neurons of cortical and hippocampal leads to memory and cognitive dysfunction [51]. Another neuropathological hallmark of AD is appearance of neurofibrillary tangles containing hyper-phosphorylated tau protein on intraneuronal paired helical filaments and extracellular plaques of β amyloid peptide (Aβ). Aβ are small fragments of amyloid precursor proteins (APP) containing 39–43 amino acids. Thus, the aggregation of small segments of Aβ (ADDLs, amyloid-β-derived diffusible ligands) are mainly responsible for memory deficits and synaptic damage in AD [52,53].

3.1. AD therapy

At present, the available therapies of AD are based on cholinergic progress, particularly on the cholinesterase (AChE and BChE) activities prohibition [54]. Although cholinergic inhibitors have greatest benefit for cognitive dysfunction, these are unable to compensate the continuous loss of hippocampal and cortical neurons. Currently the treatment of AD depends on acetylcholinesterase (AChE) inhibitors (Rivastigmine, Dopenezil, Galantamine) or NMDAR inhibitor (Memantine) indicate only momentary effect but unable to stop disease progress and mainly administered orally or transdermally [55–57].

In year 2000, Rivastigmine, a non-competitive and reversible AChE

Table 2
Advantages of different NPs for the treatment of Alzheimer's Disorder.

Type of nanoparticle	Therapeutic Agents	Preparation method	Advantages/applications	Route of administration	Reference
Polystyrene nanoparticles	Metal chelators a) Copper chelator -D Penicillamine	Conjugation of drug and nanoparticles	Deliver D-penicillamine to the brain for the prevention of Aβ (1–42) accumulation		[175]
Polystyrene nanoparticles	b) Iron chelator — MAEHP	Polystyrene nanoparticles activated by N-cyclohexyl-N_-(2-morpholino ethyl) carbodiimide methyl-p-toluensulfonate and then reacted with the iron chelator, 2-methyl-N-(2_-aminoethyl)-3-hydroxyl-4-pyridinone	Nanoparticle–chelator conjugates have the potential to inhibit Aβ fibril formation and to cross the BBB and protect human brain cells from Aβ-related toxicity		[176]
Polymeric n-butyl-2-cyanoacrylate	Quinoline derivatives — Clioquinol	Polymerization technique	Drug loaded nanoparticles exhibited specificity for Aβ plaques both in vitro and in vivo; capable of aiding in the early diagnosis of AD	i.v. injection	[177]
Chitosan nanoparticles	Hormones — Estradiol	Prepared by ionic gelation of chitosan with tripolyphosphate anions (TPP)	Chitosan nanoparticles significantly increase the transport of estradiol into the central nervous system	Intranasal administration	[178]
Poly (ethylene glycol)-poly (lactic acid) nanoparticles modified with wheat germ agglutinin	Proteins and peptides —VIP	Produced by emulsion/solvent evaporation technique	Improvement in brain delivery of estradiol using wheat germ agglutinin nanoparticles	Intranasal administration	[179]
a) Polysorbate-80 coated poly (nbutylcyanoacrylate) NP	ChEIs —Tacrine		Enhanced concentration of the drug in the brain	i.v. injection	[180]
Chitosan nanoparticles	ChEIs —Tacrine	Spontaneous emulsification method	A new drug delivery system for increasing bioavailability of the drug in the brain	i.v. injection	[170]
Core–shell nanoparticles composed of a polystyrene core and a degradable PBCA [poly (butyl-2-cyano acrylate)] shell	Amyloid β targeted drugs —Thioflavin T and S	Emulsion polymerization method	Tools to trace and clear Aβ in the brain	Intracerebro ventricular injections	[181]
Poly (n-butyl cyanoacrylate)	Rivastigmine	Emulsion polymerization method	3.82 folds increase in brain concentration of the drug	I.v. injection	[182]
Viologen–phosphorus dendrimers		Conjugation Method	Non-toxic viologen–phosphorus dendrimers inhibited the activities of both cholinesterases, showing their potential as new drugs for treating neurodegenerative diseases		[69]
Gold nanoparticle	Gold nanoparticles	AuNPs were functionalized with peptide H-Cys-Leu-Pro-Phe-Phe-AspNH2 (Cys-PEP) which was synthesized following a Fmoc strategy and solid phase synthesis, forming the conjugates AuNP–Cys-PEP	The prepared nanoparticles dissolve toxic protein deposits of Aβ1–42 (amyloid deposits) by the combined use of weak microwave fields and gold nanoparticles (AuNP) without any bulk heating		[183]
Eudragit S100 nanocapsule	Melatonin	Produced by interfacial deposition of preformed polymer	Melatonin-loaded polysorbate 80-coated nanocapsules caused a marked reduction on lipid peroxidation levels and also increased the total antioxidant reactivity in the hippocampus	Intraperitoneal injection	[184]
Chitosan nanoparticles	Amyloid beta	Prepared by a combination of mechanical stirring emulsification methods and chemical crosslinking method	Nano-vaccine delivery system could be used as a potential carrier for A beta	Systemic administration	[185]

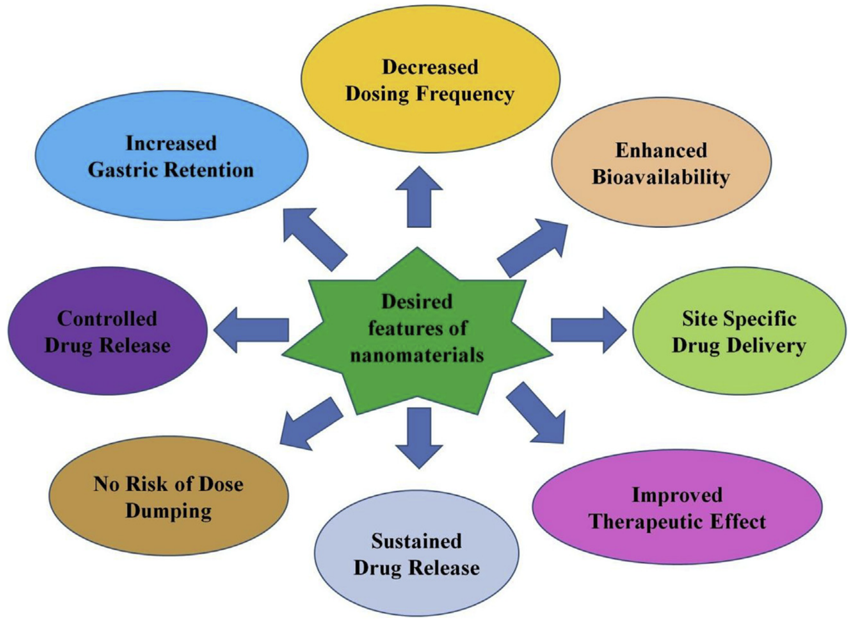

Fig. 3. Desired features of nanomaterials.

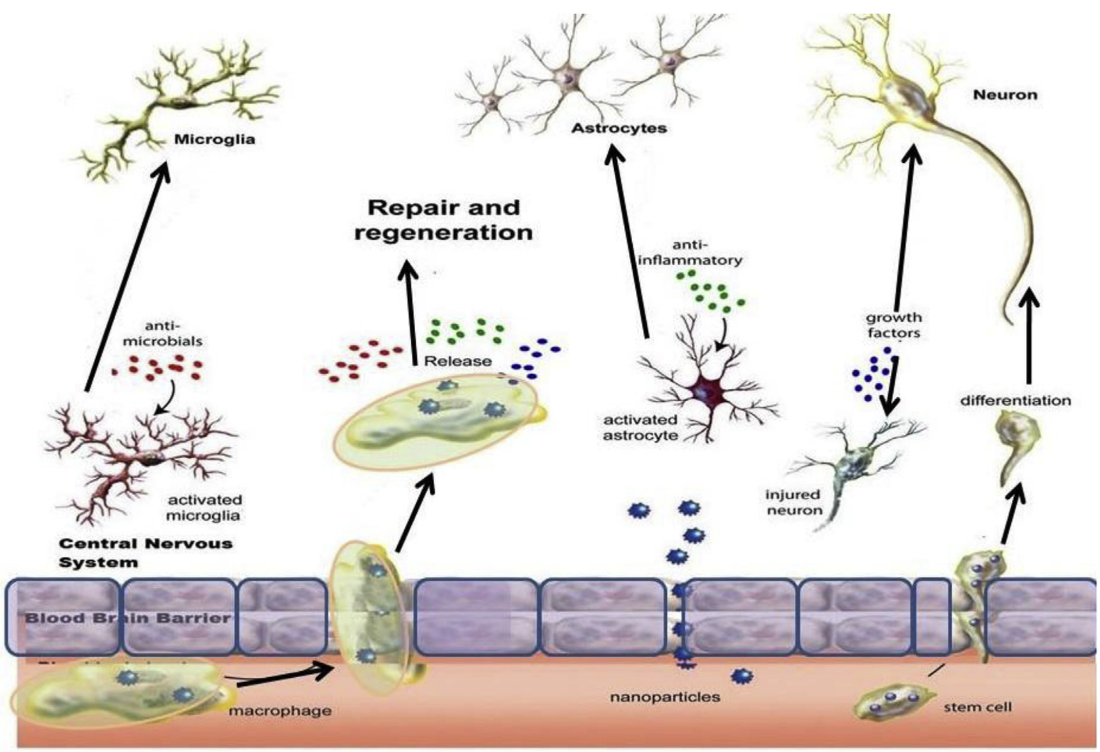

Fig. 4. Pictorial representation of treatment of neuro-diseases from nanomedicine.

inhibitor was approved by the FDA for the treatment of AD [58]. Now a day, nanotechnological strategies are employed for enhancing the potency of AD therapies (Fig. 4). The nanotechnological devices target to Aβ aggregation and fragmentation of APP, not only in CNS even in blood with the approach of reducing its level in brain [59]. The reduction of Aβ aggregation and fragmentation of APP in the brain is known as 'sink effect'. Gobbi et al. developed nanoliposomes (NLs) utilizing phosphatidic acid or cardiolipin [60]. In an another study it has been observed that these NLs have greater affinity towards Aβ and diminished the toxicity of these peptides in ex-vivo condition [61]. Canovi et al. developed NL formulation with anti-Aβ mAb, indicating higher affinity for Aβ in ex-vivo as well as in vivo studies [62]. In addition to these, Mourtas et al. developed another formulation of NL with curcumin derivative, which displayed high affinity towards Aβ and inhibited Aβ aggregation in an in vitro model [63,64].

Amyloid fibrillar deposition of misfolded proteins can be exploited for both therapy and diagnosis of AD. Recently, Orteca et al. developed structurally modified curcumin (phtalimmide derivative, K2F21) scaffold for improving its bioavailability, pharmacokinetic stability in physiological conditions, and in vitro ability to interfere with β-amyloid fibrils and aggregates at different incubation time. Computational simulations established the modification in conformational dynamics and interaction with the amyloidogenic region of the protofibril facilitating disaggregation on ligand binding. In vitro results reflected safety and protection against glutamate toxicity in hippocampal HT-22 mouse cells at 1 μM concentration. Authors claimed that the developed derivative of curcumin appeared as a promising candidate for both diagnosis and therapy of AD [65].

On the other hand, dendrimers are appeared as one of the most successful tools for the management of neurodegeneration at the nanoscale level. Dendrimers have greater capability for crossing BBB and targeted drug delivery with low toxicity [66], thus dendrimers emerge out as interesting device in treatment of NDs. It has been observed that PAMAM and phosphorus dendrimers indicated their anti-amyloidogenic activity [67,68]. Cieplucha et al. reported potential of viologen–phosphorus dendrimer for the inhibition of AChE and BChE activities and showed its caliber against AD [69]. Klajnertet al. investigated effect of 27 terminal morpholine fabricated GATG (gallic acid-triethylene glycol) dendrimer on the aggregation process of Aβ peptides. The developed formulation reduced the amount of prefibrillar forms of Aβ and ultimately lowered the toxicity of Aβ peptides [70].

On the other side, the available literature indicated the promising therapeutic potential of various growth factors and neurotrophins against the AD [71–74]. Growth factors (GFs) like insulin-like growth factor (IGF-1/IGF-2) [75,76], bone morphogenetic proteins (BMPs) [71,77,78], basic fibroblast growth factor (bFGF) [79–81] and glial-derived neurotrophic factor, GDNF [82], neurotrophins (nerve growth factors, NGF) [83–85]; and brain-derived neurotrophic factor (BDNF) [86,87] are very hopeful therapeutic molecules for the management of NDs. Lauzon et al. discussed various strategies involving specificity enhancement of growth factors (GFs) to brain and provided information regarding recent advancement for brain targeted delivery of GFs in term of *in-vivo* and *in-vitro* effect in context of AD [88]. For the treatment of AD, Yang et al. developed single-walled carbon nanotubes (SWCNTs), which successfully delivered acetylcholine into brain then SWCNTs easily entered into lysosomes and reached to targeted organelles, except mitochondria [89].

Metals like copper, zinc, iron, and aluminum promoted oxidative damage is one of the causes of AD. FDA approved D-Penicillamine, a copper chelator to treat AD. The D-penicillamine decreases the amount of metal ions, which promote the beta-amyloid deposition in AD patients. Further, it does not affect the integrity of the BBB [90].

3.2. AD diagnosis

Nanotechnology attempt more lucrative methods over conventional assays for the estimation of amyloid-beta derived diffusible ligands or tau protein (pathogenic markers) in human CSF employed in early *in-vitro* diagnosis of AD [91]. In this context, nanotechnology indicate tremendous advantage for effective imaging of CNS functions and status of diseases as well as in advance neuro surgical practices. Now a day, Magnetic Resonance Imaging (MRI) has appeared as the vital tool for the imaging of brain disorders. Positron Emission Tomography (PET) imaging also very potent in diagnosis of the various nervous system disorder's mechanisms, including the pathophysiology of AD. In this course, radio-labeled amyloid ligands tracked the pathophysiological process of AD [92–94].

Gadolinium, iron and manganese containing nanoparticles (NPs) are extensively explored for their contrast activity. Among them superparamagnetic iron oxide (SPIO) NPs have greater surface area, magnetic properties with low toxicity, create more interest in this approach. Generally, core of SPIO NPs contains a crystalline iron oxide (including magnetite, Fe_3O_4, or maghemite, γFe_2O_3), which make it biocompatible and encased in a coated monomerous polymer [95,96]. The ferumoxtran-10 (dextran coated USPIO) involved in the diagnosis of ischemic damage in patients of cerebral ischemia [97]. On the other hand, Beckmann et al. studied amyloid precursor protein mouse AD model for cerebral amyloid angiopathy and found that MRI detection of microvascular lesions in the brains of the mice was enhanced with the systemic administration of SPIOs. In case of AD, SPIO NPs s entered in the monocytes and traveled into the circulation then penetrate in the brain through chemokines due to attraction of amyloid beta (Aβ)-stimulated glial cells [98].

The clinical MRI agents like Feridex® (Endorem) and Resovist® were used as important tool for diagnosis of AD. The AMAG Pharma discontinued Feridex® in 2008, whereas in 2001, Resovist® was approved for the European market, but in 2009 its production was abdicated. Thus, essentially, a clinically active device for screening of AD should be available in the market. Li et al. reviewed various nano-approaches involved in the generation of MRI contrast agents for cell labeling and tracking [99]. Polyethyleneglycol (PEG)-coated USPIO NPs may adhere with Aβ1-42 peptides and offer a wide opportunity for simultaneous targeting and imaging of amyloid plaques in AD transgenic mice. Thus, intravenous injection of these NPs transiently opens the BBB for detection of the level of amyloid plaques [100]. On the other hand, ultrasensitive immunosensors involve surface plasmon resonance for the detection of Aβ peptides [101]. While scanning tunneling microscopy utilize specific immobilized mAb fragments on the surface of gold nanoparticles (Au NPs) for recognition and lead to electrical detection [102]. Yang et al. synthesized and marked out Aβ-40 or Aβ-42 antibodies coated with some specific SPIO and applied them in the immunoassay of AD [102]. Neely et al. developed and characterized anti-tau antibodies coated Au NPs involved in two-photon Rayleigh scattering assay for the detection of CSF tau proteins [103].

Moreover, in the clinical diagnosis Aβ-40 or Aβ-42 peptides levels involve a comparative estimation of these peptides in normal and AD patients. The Aβ screening methods involved electrochemical sensing of saccharide–protein interactions, has also been reported [104]. In addition, with this context, Georganopoulou et al. have established ultrasensitive assay [105], for the determination of approximate ADDL concentration by utilizing Au NP bio-barcode. for the detection of tau protein, While Neely et al. [103] utilized photons coupled antibody coated Au NP. Recently, nano-HPLC-MS technologies also have been used as possible additional pathogenic marker of AD and are involved in phospholipid profiling of CSF, providing an opportunity to follow lipid changes [106]. On the other hand, streptavidin conjugated quantum dots (QDs) indicated a high sensitivity for the recognition of AAP for the *in-vitro* estimation in comparison with conventional fluoro immunoassay [107].

While *in-vivo* nanotechnological approaches involve the estimation of Aβ deposits in the brain, the deposition of β amyloid protein in AD transgenic mice was detected from μ MRI technique which involved Aβ-coupled iron oxide NP either superparamagnetic or mono crystalline form [108]. Roney et al. synthesized polymeric n-butyl-2-cyanoacrylate NP enclosed with the radio-labeled drug ^{125}I-CQ which has affinity towards amyloid proteins [109]. The obtained results indicated the BBB crossing ability of NP with rapid transportation and retention in the AD transgenic mice brain in comparison of controls.

4. Nanotechnology for Parkinson's disease

PD lead a progressive loss of neurons of specific areas of brain approximately 1–2% of the population of age ≤ 65 years is affected from PD disorder in the world [110]. PD involve the loss of dopaminergic neurons in the substantia nigra and pars compacta and results of difficulties in the movement control. The appearance of Lewy's bodies in the brain of PD patients is the primary sign of this disorder. The Lewy's bodies contain 50–700 nm long filaments of the α-synuclein proteins as cytoplasmic inclusions. Various cellular mechanisms such as ER stress, proteasomal and mitochondrial dysfunction are behind of neuronal death in PD [111].

4.1. PD therapy

At present, very limited supportive care, management and cure is available for PD. All these situations slow down the treatment and therapy of PD and alleviate the progression of disease. The available pharmacological treatment and therapy mainly pay its attention on restoration of dopaminergic neurotransmission [112].

Nanotechnological approaches lead a safe and effective strategic resolution over the available conventional approaches for the best remedy of PD. Tiwari et al. synthesized nicotine-encapsulated poly(lactic-co-glycolic)acid (PLGA) nanoparticles. At nanosize the bioavailability of nicotine enhanced with consequent decrease in the oxidative stress and apoptosis with an improved neuroprotective efficacy [113]. Recently Gerardo Leyva-Go´mez et al. presented an overview on technical aspects for drug delivery to the brain from the NPs. The study involve analysis of surface phenomena which are involved in functional development and synthesis of NPs for the treatment of PD [114]. Trapani et al. prepared specific chitosan NPs with an external DA coating. *In-vivo* experiments on rats indicated that on intraperitoneal administration, DA loaded chitosan NP have less cytotoxicity with greater penetration to the striatum more than DA alone [115]. Huang et al. found a significant improvement in locomotor activity as well as minimization of dopaminergic neuronal loss, with the increase in DA levels in PD rat brain through the administration of human neurotrophic gene encapsulated in lactoferrin–modified NP [116]. In a study it has been observed that Odorranalectin (OL) NPs are act as potential carriers for the delivery of special macromolecular drugs from olfactory route to brain for the treatment of PD [117]. Hu et al. developed lactoferrin (Lf) conjugated polyethylene glycolpolylactide-polyglycolide (PEG-PLGA) nanoparticles (Lf-NPs) as a novel biodegradable brain drug delivery system, indicate auspicious drug delivery with less toxicity [118]. On the other side, various cationic dendrimers mark their candidature among the new pharmacological strategies against neurodegenerative disorders with the prevention of proteins fibrillation specially α-synuclein fibrillation in the NDs [119–121]. Many times, dendrimers can also alter functions of different proteins i.e. viologen-phosphorus dendrimers modified the activities of AChE and BChE [122]. Recently, it has been investigated that carbosilane dendrimers prevented the α-synuclein fibrillation for the rotenone-induced damage of hippocampal cells (mHippoE-18) in the rat brain. An another study indicated a broad contribution of dendrimers in the increased vitality, potentiation of mitochondrial membrane activity and decreased reactive oxygen species level in the cells of specific parts of the brain [123].

It has been found that exosomes from blood exhibit natural brain targeting ability by transferrin-transferrin receptor interaction. In this regard recently, Qu et al. developed dopamine loaded biocompatible, spherical blood exosomes of 40 and 200 nm size range for delivering drugs across the BBB. In vivo studies demonstrated that the blood exosomes successfully delivered dopamine to brain as witnessed by > 15-fold increased dopamine brain distribution [Fig. 4]. Dopamine-loaded exosomes showed lower systemic toxicity as compared to free dopamine and improved therapeutic efficacy in a PD mouse model [124].

4.2. PD diagnosis

The clinical sign of PD include loss of more than 50% of the dopaminergic neurons and 75–80% of striatal dopamine in the brain [125–127]. Thus, PD must be detected in early stages for proper treatment. At this stage, the progression of PD can be easily suspended from the neuroprotective medicines, so the availability of a novel biomarkers for early detection of PD can help in its diagnosis and treatment [128,129]. Recently, Qiang et al. described clinical, neuroimaging, biochemical, genetic and proteomic biomarkers, which are involved in PD diagnosis and treatment. Single photon emission computerized tomography (SPECT), used for estimation of dopaminergic pathways in the brain may be useful to diagnose PD [130]. In a recent study, Akhtar and Stern, described early symptomatology of Parkinson's at-risk syndrome with the broad study of disease biomarkers and putative disease-modifying therapeutics used for PD. They compared clinical diagnosis, radiological screening and molecular examinations involved in the early detection of PD [131].

Now a days nanotechnological approaches possess their effectiveness in diagnosis and imaging of PD. In this sequence, An et al. tapped high sensitivity photo electrochemical immunosensor, Au-doped TiO_2 nanotube (NT) arrays to trace α-synuclein proteins in CNS [132]. Previously, Baron et al. developed Au NP with plasmon absorbance involved in an *in-vitro* quantitative estimation for neurotransmitters involved in PD pathology [133].

5. Nanotechnology for prion disease (PrD)

PrD lead to stockpiling of misfolded Prion Protein (PrP) isoforms, PrD included a bunch of NDs. First identified prion disease in human was Creutzfeldt-Jakob disease. It is found periodically and about one case per million individuals per year is observed. In the sane individuals, cellular isoform (PrPC) of prion protein exists two large alpha-helical structures. While in the pathogenic protease-resistant isoform (PrPSc), predominant β-sheet is found that may produce toxic amyloid aggregates. When a pathogenic isoform has been originated, PrPC modified into PrPSc via protein-protein interaction [134].

5.1. Prion disease therapy

Many *in-vitro* studies showed that different types of polyamine dendrimers are retracting pathogenic prion isoform (PrPSc) from lysosomal degradation and eradicate them from infected cells. The different polyamines have positive charges over them and their action depend on this positive charge. Lim et al. synthesized less toxic positively charged polyamines with greater potential [135]. Ai Tran et al. synthesized polyelectrolyte multilayer-coated Au NP containing sulfonates and primary amines as functional groups on the surface with a great therapeutic relevancy and inhibited to PrPSc aggregation in neuroblastoma cells at very low dose [136]. Sousa et al. [137] indicated that Au NP coated with the similar groups have crossing ability across the murine BBB and enter the specify neuronal structures in which PrP agglutination occurs. On the other side, McCarthy et al. on the bases of dendrimer/prion interactions, formulated a new working model which indicated that dendrimers destabilize the prion protein and rendering it susceptibility to proteolysis thus eliminate PrP(Sc) [138]. In another study, it has been found that dendrimers inhibited the intracellular conversion of PrPC to PrPSc while anti-prion activity is independent from their cationic surface charges. This work indicate inhibitory action of mPPI G5 dendrimers against the conversion of PrPC to PrPSc and also determine the effect of other drugs which are enhancing this action of mPPI G5 dendrimer [139].

5.2. Prion disease diagnosis

Xiao et al. developed a novel diagnostic approach, involving two different type of aptamers which were able to recognize various epitopes of PrPSc and segregate PrPSc from PrPc in serum as well as in brain homogenate [140]. In this approach, the aptamers were attached to the surface of QDs and magnetic micro particles, in presence of PrPSc. These produced a highly fluorescent sand which like structure in aqueous medium and it can be easily isolated under the influence of external magnetic field. Xie et al. demonstrated *in-vitro* site-specific labeling of PrP expressed on cell surfaces from PEG-interspersed nitrile triacetic acid-functionalized QDs [141].

6. Nanotechnology for amyotrophic lateral sclerosis

Amyotrophic Lateral Sclerosis (ALS) lead to fatal neurodegeneration and affect approximately 1–2/10,0000 person per year. The signet of this disorder includes paralysis of voluntary muscles from the selective death of motor neurons in the brain and spinal cord. The mutations in SOD1 gene which encode superoxide dismutase enzyme is the main cause of ALS in approx. 20% of familial ALS cases. The mutated SOD1 gene leads to formation of toxic free radicals and intracellular aggregates that restrict chaperone or proteasome activity, with consequent mis-folding and inadequate expulsion of manifold proteins [142].

For the specific treatment of ALS, Bondì et al. synthesized riluzole solid lipid NP with high drug loading capacity and a greater efficacy than free riluzole. The higher drug loading capability with greater carrying capacity of riluzole solid lipid NP into the brain with lower indiscriminate bio distribution in rats open an another route for the use of NP for ALS therapy [143].

Recently, a rat model of ALS detection involved administration of T cells labeled USPIO NP in the MRI technology. The study revealed an infiltration of $CD4^+$ lymphocyte in the midbrain/interbrain, while $CD8^+$ cells were more confined to the brainstem region [144]. Machtoub et al. for the detection of the pathological regions in ALS rat brain, injected USPIO NP conjugated with anti-CD4 antibodies from intravenous route [145].

7. Nanotechnology for neuroprotection and neuronal tissue regeneration

7.1. Neuroprotection

Most of the time, a higher level of reactive oxygen species is involved in CNS injuries. It has been observed that multiple radicals able to incorporate per-molecule similar as radical sponges, but a delocalized π double bond system eradicate superoxide radicals over the dismutation catalytic mechanism [146]. A study indicated that a trismalonic acid derivative of the fullerene C60 molecule (C3) is able to raise the life span of mice about 300% while lacking mitochondrial manganese superoxide dismutase (MnSOD) [147]. On the other hand, cerium oxide NP (nanoceria) are established as neuroprotective agents lead to higher antioxidant properties and guard the cells from death due to oxidative stress shown in *In-vitro* experiments on isolated rat spinal cord neurons [148].

7.2. Neuronal tissue regeneration

The strategies for repair of damaged neuronal tissues involve the extracellular scaffolds which attached neuronal tissues and facilitate axonal growth. Neurotrophins (NT) and nanofibres (NF) have structural similarities with neuronal tissues, widely used as regenerative medicines. Jin et al. [149] recently synthesized a multi-walled carbon nano tube coated with electrospun poly (l-lactic acid-co-caprolactone) NF, indicated its potential for the prohibition of outgrowth of neurite in *in-vitro* experiments. On the other side, NT/NF both are utilized as scaffold and carrier for neurotrophin delivery, thus are involved in promotion, proliferation and differentiation of neurons. *In-vivo* experiments indicated that the incorporating potential of NF for nerve growth factor lead to effective regeneration and promotion of sciatic nerve [150]. One another approach leads to synthesis of electrically conducting NT/NF scaffolds for the enhancement of the regenerative processes with the future aspect for potentiating brain circuit activity. Electrically conducting nano-scaffolds broadly used in electrical stimulation of nerve stem cells due to their low obstruction and high charge transfer abilities [151]. Lee et al. in a combined approach, synthesized PLGA NF with electrically conducting polypyrrole covering which in *in-vitro* experiments act with nerve growth factor and lead neurite formation and outgrowth [152].

8. Neurotoxicity of NM

In spite of greater potential of NM in the field of biomedical, there is some possible toxic effect of NM also observed on CNS [49,137,153]. The available data indicated that various factors including shape, surface area, surface charge, size, chemical composition are responsible for toxicity of NM. At the latest, on the bases of surface chemistry (bare, \NH_2 or\COOH functionalized) SPIONs has been investigated *in-vitro* neurotoxicity of on human neuroblastoma cell line at both cellular and molecular levels. It has been observed from MTT assay that the bare SPIONs have greater toxicity than those coated SPIONs, due to their increased tendency for absorption capability to vitamins, amino acids, and ions, leading to changes in pH and composition in cells and cell medium. DNA micro array experiments manifested that SPIONs-COOH provoke the up regulation of oxidative stress-inducible genes [154]. Various factors like size, shape (spheres, rods, and urchins)and surface coating (PEG or acetyl trimethyl ammonium bromide) of gold NP has been investigated via *in-vitro* and *in-vivo* experiments in term of their neurotoxicity.

Positively charged Au NPs exhibited toxicity on microglia and neurons during *in-vitro* experiments, independently of the shape. The intranasal administration of Au NPs during *in-vivo* experiments induced TLR-2 promoter activity and transient microglia activation in transgenic mice. The induction and the affinity depended on shape and surface of NP. Moreover, it has been observed that spheres, in particular 50 nm sized Au NPs indicated significantly great extent of cell interactions than rods [155].

For the investigation of neurotoxicity of commercially available NTs, PC12 cells are is commonly used *in-vitro* model for neuro toxicity studies. During an experiment, it has been observed that NTs decreased PC12 cell viability and mitochondrial membrane potential, dependent on time and dose while an increase in ROS production, the cell cycle arrest in the G2/M phase and the apoptotic rate depend only on the dose of NTs [156].

Zhang et al. found that the exposure of TiO_2 NP lead morphological changes of cortex neurons and disturb the levels of monoamine neurotransmitter in the sub-brain areas [8,157]. At the beginning some NP, indicated promising features in therapy and diagnosis but simultaneously their toxicity in the *in-vivo* experiments limited their clinical use. In the case of QD and NTs, repeated *in-vivo* toxicity limited their future use at the level of in vitro diagnosis. Thus, the benefit-risk balance should be carefully evaluated for nano technological approaches promised for brain drug delivery and diagnostics.

9. Recent advancement in therapeutic strategies of neurodegenerative disorders

9.1. Cannabinoid therapeutics

The classic hallmarks of the aged brain and neurodegenerative conditions involve abnormal protein accumulation, impaired lysosomal system, oxidative stress, excitotoxicity, and neuroinflammation [158]. The endocannabinoid system (ECS) has been emerged as a viable target for symptom alleviation or disease progression based on pharmacological modulation of endocannabinoid signaling, which involves both cannabinoid receptor-dependent effects and cannabinoid receptor independent effects [159]. The cannabinoid receptor-dependent effects are (i) activation of cannabinoid type-1 (CB1) receptors to normalize glutamate homeostasis or to activate autophagy; (ii) activation of cannabinoid type-2 (CB2) receptors and peroxisome proliferator-activated receptor γ (PPARγ); (iii) modulation of G-protein receptor 55 (GPR55) to reduce local inflammatory events [160].

9.2. Human fetal neural stem cell therapy

Clinical trials using primary brain fetal tissue demonstrated the suitability of neural stem cell (NSC) therapy for neurodegenerative diseases. Based on supportive, preclinical proof-of-principle data, up to 21 somatic stem cell-based pilot trials have been developed for the treatment of ALS [161]. Immune-deficient models represent one of the elective experimental paradigms for the analysis of putative tumorigenicity of hNSC in vivo. Three of those studies have used hNSC lines: NCT01640067, NCT01348451 and NCT01730716. Interestingly, all the studies confirmed no acceleration in the course of the disease; on the contrary some of the patients showed a transient improvement of motor functions and ALS-FRS scale [162–164]. Although the data are encouraging, however this type of conclusions should be addressed more properly in larger phase II/III trial.

9.3. 3D human brain cell models for neurodegenerative diseases

Reason behind a high degree of failure in many recent clinical trials for disease-modifying therapeutics is the difficulty of translating findings from animal-based cell models to human patients. The majority of non-animal neurodegenerative disease research has been conducted in 2 dimensional (2D) models of rodent neonatal neurons and glia. The human stem cell technologies combined with microfluidic technologies have opened the door to development of patient-derived 3D brain cell models with the advantage in providing a micro-physiological system more closely reflecting the in vivo brain environment, and promote the interaction between different patient-derived brain cell-types. The new patient derived 3D brain cell systems will likely improve translational outcomes for disease therapeutics [165].

10. Perspectives and conclusion

Nowadays, scientists are investigating molecular, cellular and circuit functions of the CNS for the identification of causes and the pathways involved in neurodegeneration. The nanotechnological approaches are very progressive from the last few years in the direction of diagnosis and treatment of neurodegenerative disorders. However, more endeavors will be required in this arena for the conversion of preclinical experiments to substantial clinical exercises.

This is an arduous challenge for researchers, to develop feasible, compatible and acceptable theranostic NM for neurodegenerative disorders. Currently used magnetic ones indicated a successful candidature as theranostic due to their magnetic properties that may be utilized for MRI, tissue engineering and cell tracking, targeted drug and gene delivery systems. Recently, nanotechnology continuously working for development of novel tools which will emerge new insights in treatment and diagnosis of NDs.

Disclosures

There is no conflict of interest and disclosures associated with the manuscript.

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